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10/520,781	01/11/2005	Yoshihiro Urade	2005_0021A	2424

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EXAMINER	
JEAN-LOUIS, SAMIRA JM	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,781	URADE ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-7 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-7 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continuation Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/21/09 has been entered.

Response to Arguments

This Office Action is in response to the amendment submitted on 01/21/09. Claims 3-7 and 10 are pending in the applications, with claims 1-2, 8-9, and 11-13 having being cancelled. Accordingly, claims 3-7 and 10 are being examined on the merits herein.

Receipt of the aforementioned amended claims and declaration of Dr. Yoshihiro Urade is acknowledged and has been entered.

Examiner further acknowledges amendment of claims 3 and 10 which now recites the specific DP-type and CRTH2 antagonists of prostaglandin D2 receptors as opposed to all prostaglandin D receptors. Thus, the examiner contends that in light of such amendment, the rejection under 35 U.S.C. § 112, first paragraph is hereby withdrawn.

Applicant's arguments with respect to the rejection of claims 3-7 and 10 under 35 U.S.C. §103(a) rejection has been fully considered but is not found persuasive. Applicant argues that based on the 5 references provided in the December 16, 2008 reply, a person skill in the art would have no reasonable expectation of success in using the claimed compounds to inhibit injury based on the finding that a compound was effective for treating edema of nose and respiratory organs. Such arguments however are again not persuasive as the Examiner clearly established a *prima facie* case of obviousness against the aforementioned claims. Specifically Tsuri et al. teach compound (ZS)-7-[(1R,2R,3S,5S)-2-(5-hydroxybenzo[b]tiophen-3-ylcarbonylamino)-10-norpinan-3yl]hept-5-enoic acid obtained via the modification of compound 14 using R-group 19 and compound (ZS)-7-[(1R,2R,3S,5S)-2-(5-benzo[b]tiophen-3-ylcarbonylamino)-10-norpinan-3yl]hept-5-enoic acid obtained via modification of compound 14 using R-group 18 and further teach such compounds as potent selective antagonists of prostaglandin D2 receptors. Tsuri et al. additionally teach that these compounds are effective in reducing intranasal pressure largely due to their inhibition of vascular permeability (i.e. edema), effective in reducing smooth muscle cell contractility (i.e. cells found in vascular cells) as well as effective in reducing the number of immune cells infiltrates (i.e. eosinophils). Consequently, these data suggest that the aforementioned PGD2 receptor antagonists are helpful in reducing inflammation, edema, and vascular permeability. In the specification, Applicant defines treatment of brain injury as encompassing brain edema, cerebral bleeding (which occurs as a result

of vascular permeability), and as encompassing cerebrovascular disorders (see pg. 3, lines 20-24).

Wong et al., on the other hand, teach the pathophysiology associated with primary brain injury. Following brain injury, a primary inflammatory response is triggered which then increases vascular permeability (i.e. cerebral bleeding) and vasodilation and which subsequently leads to vasogenic edema, cerebral ischemia and impaired autoregulation. Furthermore, the vasogenic edema subsequently results in cytotoxic edema that exacerbates the existing cerebral ischemia resulting in secondary brain injury. Thus, in view of applicant's definition of what a treatment of brain injury entails and in view of the disclosures of Tsuri and Wong, one of ordinary skill in the art would have found it obvious to utilize the compounds of Tsuri et al. given their efficacy in inhibiting increases in microvascular permeability and their efficacy in reducing inflammation due to their effects on eosinophils. Moreover, one of ordinary skill in the art would have found it obvious to utilize the aforementioned compounds in the treatment of brain injury as brain injury is characterized by inflammation, edema formation and vascular permeability and Tsuri teaches that the instantly claimed compounds were effective in attenuating edema, vascular permeability and inflammatory responses. As for Dr. Urade's Declaration, while the experiment utilizing prostaglandin D receptor antagonists TM30089 and ONO-1427Na demonstrated a reduction in brain leakage, such results however do not negate the obviousness of the claims (i.e. obvious to try) wherein one of ordinary skill in the art would have found it obvious to try the compounds of Tsuri for reducing edema and vascular permeability, all

components involved in brain injury as defined by applicant's specification. Thus, the Examiner contends that regardless of the localization of the injury, the process of inflammation is characterized by the same steps and therefore the effects of the compounds would necessarily be expected to result in a successful inhibition and/or attenuation of such symptoms. As a result of the combined teachings of Tsuri in view of Wong, claims 3-7 and 10 are indeed rendered obvious and the rejection is therefore maintained.

For the Foregoing reasons, the rejection under 35 U.S.C. §112, first paragraph is hereby withdrawn. The rejection under 35 U.S.C. §103(a) is maintained for reasons of record. However, in view of applicant's amendment, the following modified 103 (a) Non-Final rejection is being made.

Claim Objections

Claims 4-7 are objected to under 37 CFR 1.75 (c), as being of improper dependent forms for depending on rejected claims. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In particular, claims 4-7 are dependent on claim 3 which stands rejected under 35 U.S.C. § 103(a). Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-7 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method for treating brain injury administering DP-type or CRTH2-type prostaglandin D receptor antagonists, does not reasonably provide enablement for a method for inhibition of brain injury. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to a method for treatment or inhibition of a brain injury which comprises administering an effective amount of prostaglandin D receptor antagonists to a patient in need thereof. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention for inhibition of brain injury using DP-type or CRTH2-type prostaglandin D receptor antagonists. Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdAPIs 1986) at 547 the court recited eight factors:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention:

The instant invention pertains to a method for treatment or inhibition of a brain injury which comprises administering an effective amount of prostaglandin D receptor antagonists to a patient in need thereof. The invention requires that one of skill be able to inhibit brain injury utilizing DP-type or CRTH2 type prostaglandin D receptor antagonists without empirical, undue and unpredictable trial and error experimentation; i.e., the skilled artisan must be able to readily recognize what structural features confer the antagonist properties of the prostaglandin D receptors to inhibit brain injury and create another antagonist with the same desired characteristic. However, given that applicant fails to enable and demonstrate inhibition of brain injury, one of ordinary skill would not readily envisaged inhibition of brain injury utilizing a prostaglandin receptor antagonist without undue experimentation.

Scope of the invention:

Since the instant specification provides no limiting definition of the term “inhibition

of brain injury", the examiner will adopt the broadest reasonable interpretation for same. Webster's Ninth New Collegiate Dictionary defines "inhibition" as "restraining of the function of a bodily organ or an agent", i.e., to restrain the occurrence of a brain injury.

The scope of the invention is thus very broad, encompassing restriction to prevention of a brain injury utilizing certain prostaglandin D2 receptor antagonists. However, there is no description or teaching of inhibition of a brain injury except for inhibition proffered by the antagonists themselves and which do not completely restrain or prevent the occurrence of a brain injury. As such the skilled artisan cannot make the broad scope of the claimed invention.

State of the prior art:

The state of the art with regard to inhibition of a brain injury is poorly developed. No prior art exists specifically inhibiting brain injury as a therapeutic modality in humans.

Relative skill of those in the art:

The relative skill of those in the art is high, typically requiring an advanced professional degree.

Predictability or lack thereof in the art:

The skilled artisan would view that the method for inhibition of brain injury by administering prostaglandin D (PD) receptor antagonists as being unpredictable due to lack of prior art and the fact that one cannot inhibit occurrence of brain injury especially

since genetic and happenstance factors are involved in the occurrence of such injury. The state of the prior art itself in regard to the localization or distribution of prostaglandin D receptors in human tissues is a topic of much debate. Initial findings suggested PGD receptor localization limited to the retina and the small intestine; yet, other studies suggested PGD receptor expression on vascular smooth muscle cells as well as localization on T-helper 2 cells. At the time of applicant's invention, the field of prostaglandin D receptor localization and pharmacological development of these receptors was in its infancy of development. As such, the teachings required by applicant to make and use the such prostaglandin D receptor antagonists is great, because of the variability found in the prior art with regard to prostaglandin D receptor localization as well as inhibition of brain injury rendering the expectation of success to be low. While Applicants do teach inhibition of activation of PGD receptors, applicants fail to describe and demonstrate how such inhibition results in inhibition of brain injury. Moreover, the fact that inhibition of brain injury itself is not taught in the prior further suggests that undue burden is needed to delineate how the PD receptor antagonists achieve such inhibition. Thus without specific teachings by applicant that provide the necessary examples and show the reproducibility of such findings with CRTH2 receptors and PGD antagonists, it must be considered unpredictable as to how such inhibition occurs.

Amount of guidance provided by the inventor and existence of working examples:

In the instant case, 9 working examples are provided in the specification and 27 Figures

are included of which 6 (Figures 16, 20 and 24-27) are directly applicable to the PGD2 antagonist. Review of the examples and data provided corresponding to the claimed method of administering a prostaglandin D2 receptor antagonist for inhibition of brain injury include the DP-receptor antagonists BW-A868C, pinagladin, and ramatroban; however, these examples do not specifically include any indication as to how the effects those prostaglandin D receptor antagonists result in inhibition of a brain injury.

Although Applicant convincingly demonstrates that brain injury results in increased plasma exudate in the brain parenchyma via a time-dependent manner and results in increased infiltration of inflammatory cells, Applicant fails to demonstrate that DP-receptors result in inhibition of brain injury. For example, pretreatment of mice with DP receptor antagonists BW-A868C or ramatroban or pinagladin fail to completely, or totally eliminate all dye leakage (see Figures 24 and 27) or eliminate inflammatory cell infiltration into the injury site as shown in Figures 16 or 25. Together these data suggest a role for the DP receptor in some aspects of plasma exudation in sites of brain injury and inflammatory cell infiltration and thus **inhibition of these receptors** would necessarily help in treating brain injury, but do not convincingly demonstrate inhibition of a brain injury. Thus, none of the working examples provided teaches a skilled artisan how to inhibit brain injury via blockade of DP or CRTH2 receptors. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP §2164.

Genetech, 108 F.3d at 1366, states "a patent is not a hunting license. It is not a reward

for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague limitations of general ideas that may or may not be workable.

Therefore, in view of the Wands factors, e.g., the lack of direction or guidance provided, absence of working examples, and the lack of predictability of the art as discussed above, to practice the claimed invention herein, an artisan would have to engage in undue experimentation to test whether administration of DP or CRTH2 prostaglandin D receptor antagonists could in fact be administered to inhibit brain injury with no reasonable expectation of success. To do so, an artisan would be required to assess any and all mechanisms by which brain injury may occur and verify that the claimed invention does, in fact inhibition of brain injury, and have to do so with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-7 and 10 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Tsuri et al. (J. Med. Chem. 1997, Vol. 40, pgs. 3504-3507, previously cited) in view of Wong (Critical Care Nurse, 2000, Vol. 20. No. 5, pgs. 18-27, previously cited).

Tsuri et al. teach highly active compounds (ZS)-7-[1R,2R,3S,5S)-2-(5-hydroxybenzo[b]tiophen-3- ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid obtained via modification of compound 14 using R-group 19 (see p. 3505) and (ZS)-7-[1R,2R,3s,5s)-2-(5- benzo[b]tiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid obtained via modification of compound 14 using R-group 18 (see p. 3505). Tsuri et al. additionally teach testing of these compounds using an *in vivo* rhinitis model which showed 78% inhibition of intranasal pressure induced by antigen challenge in guinea pigs (see p. 3505, Table 2, compounds 16, 19 and 20). Administration of DP antagonists including (ZS)-7-[1R,2R,3S,5S)-2-(5-hydroxybenzo[b]tiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid reduced intranasal pressure largely by inhibiting vascular permeability (i.e. edema) and via prevention of airway resistance (see p. 3506, Table 3) as well as reduced number of immune cell (i.e. eosinophil) infiltrates (p. 3506, co1.1, lines 35-44).

Thus, these data suggest that PGD2 antagonists have promise for alleviating allergic diseases by reducing inflammation, edema, eosinophil infiltration and bronchial smooth muscle contraction.

Tsuri et al. do not teach use of PGD2 antagonists in a method for treatment or inhibition of brain injury.

Wong teaches the pathophysiology associated with primary brain injury. Following brain injury, a primary inflammatory response is triggered which increases vascular permeability and vasodilation that leads to vasogenic edema, cerebral ischemia and impaired autoregulation and which then leads into a cyclical pattern of reduced ATP and increased lactic acidosis, increased ion and water influx into cells. This cyclical pattern then results in cytotoxic edema that exacerbates the existing cerebral ischemia and further results in secondary brain injury (see p. 18, col. 3; p. 19, col. 1-2; and p.20, Figure 1).

Consequently, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the PGD2 receptor antagonists of Tsuri et al. for treatment and inhibition of brain injury because of the anti-inflammatory properties of these drugs disclosed in Tsuri and in view of the disclosure of Wong who teaches that brain injury is characterized by edema, vascular permeability, and inflammatory responses. Moreover, in view of applicant's own disclosure which states that the treatment of brain injury is analogous to treatment of brain edema and cerebral bleeding (see specs., pg. 3, lines 20-24), one of ordinary skill in the art would have found it obvious to utilize the compounds of Tsuri et al. given their efficacy in inhibiting increases in microvascular permeability (i.e. suppression of cerebral bleeding) and their efficacy in reducing inflammation due to their reductive effects on eosinophils. Moreover, one of ordinary skill in the art would have found it obvious to utilize the aforementioned compounds in the treatment of brain injury as brain injury is characterized by inflammation, edema formation and vascular permeability. Therefore, it would have

been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the Prostaglandin D receptor antagonists taught by Tsuri et al. in a method to treat a head injury in a patient in order to reduce the possibility of inflammation-induced secondary brain damage resulting from vasogenic and cerebral cytotoxic edema as taught by Wong with the end result being that of applicant's claimed invention (claims 3-6 and 10).

Finally, compounds 18-22 (Scheme 3, see p. 3505) taught by Tsuri et al. teach similar compounds to the prostaglandin D receptor antagonist structure I-Aa as in the instant claim 7 except for the stereochemistry. The difference in stereochemistry is an obvious variation as Tsuri et al. teach similar stereochemical substitutions for the other compounds found in Schemes 1 and 2, and thus it would have been obvious to make similar substitutions in the compounds made using Scheme 3. In lieu of a showing of unexpected results, one of ordinary skill in the art at the time of the invention would have had a reasonable chance of success to make and use this chemical structure using routine substitutions as are taught by Tsuri et al.

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th. If

attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

04/15/09

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617